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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/042,583	03/17/98	NI J	PF366

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STERNE,KESSLER,GOLDSTEIN & FOX
1100 NEW YORK AVENUE, N.W.
SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	
KAUFMAN,C	
ART UNIT	**PAPER NUMBER**
1646	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/042,583	Applicant(s) NI, ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *26 October 1999* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-224* is/are pending in the application.

4a) Of the above claim(s) *60,79,150,167,203 and 223* is/are withdrawn from consideration.

5)☒ Claim(s) *35,39-46 and 49-57* is/are allowed.

6)☒ Claim(s) *36-38,47,48,58,59,61-78,80-149,151-166,168-202,204-222 and 224* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *35-224* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

The amendment filed 10/26/99 has been entered.

Election/Restrictions

Newly submitted claims 60, 79, 150, 167, 203 and 223 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The method of using the host cell to screen for ligand binding is classified differently: 435/7.2 and requires a different search than that required for the nucleic acid, vector and host cell. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims drawn 60, 79, 150, 167, 203, 223 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the search and examination of the subject matter of all groups would not be a serious burden on the Examiner because, for example, references disclosing nucleic acids normally disclose the amino acids encoded by them. This is not found persuasive because the inventions are distinct for the reasons given in the previous Office acting, including their different classifications, and also references disclosing nucleic acids will often disclose a *deduced* amino acid sequence, which is not the same as disclosing the actual encoded protein. A search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention and therefore requires a search of relevant literature in many different non-overlapping areas for each invention.

The requirement is still deemed proper and is therefore made FINAL.

Response to Arguments

Applicant's arguments filed 10/26/99 which do not pertain to the new claims are moot in view of the cancellation of the previously pending claims.

The requirement for biological deposit for ATCC #97920 has been met with the submission of Statement Concerning the Deposited cDNA clone (paper #10).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Oath/Declaration

The copy of the oath or declaration submitted as Exhibit C on October 26, 1999, satisfies the requirement for a complete declaration.

Drawings

Figure 1 of the instant application is presented on two separate panels. Applicants intention of filing corrected drawings upon allowance of claims is acknowledged.

Response to Declaration

The Declaration submitted under 37 CFR 1.132 filed 10/26/99 is insufficient to overcome the rejection of claims based upon GenBank Accession AA 223122 as set forth below in view of the new claims because: It is not signed by all inventors and there is no indication that inventors Yu and Su were not inventors for the subject matter claimed. Additionally, the two IRIS electronic notebook pages did not accompany the declaration either in Exhibit A as indicated on page 2 of the declaration or elsewhere in the papers filed 10/26/99, so there is no factual showing of possession.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 36, 47-48, 63, 66-67, 82, 85, 97, 100-101, 115, 118-119, 133, 137-138, 207, 209-211 and dependent claims 37-38, 58-59, 61, 64, 77-78, 80, 83-84, 93-95, 98-99, 111-113, 116-

117, 129-131, 134, 148, 151, 221-222 and 224 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Dependent claims reciting "said nucleic acid" are indefinite because the claims upon which they depend recite two nucleic acids and it is unclear which is intended. While the use of "said reference nucleic acid" is clear, it is not clear that "said nucleic acid" refers to the non-reference nucleic acid. This rejection could be obviated by, for example, referring to the nucleic acids as the "first" and "second" nucleic acid in the independent claims, so that dependent claims could refer back to "said first..." or "said second...."

Claims 47,... are indefinite because it is not clear what a TNF ligand is. It is unclear if it is something that binds TNF or is a ligand for what TNF binds. The term is further unclear because Example 6 of the instant specification shows that DR5 does not bind TNFα. It is not clear if TNFα is intended to be a TNF ligand.

Claim 169 is indefinite because a polypeptide is not encoded by amino acids (line 4). It may comprise or consist of specified amino acids.

Claim Rejections - 35 USC § 112, First Paragraph

Claims requiring the ability to encode a polypeptide that induces apoptosis or binds an TNF ligand and claims depending thereon, (*e.g.*, 66, 67, 77, 78, 80, 85, 86, 90-95, 100, 101, 111-113,...) excluding claims 47, 48 and dependent claims, and claims 190-191 and 204 as they relate to polynucleotides with non-coding (*i.e.*, complementary) strands encoding a polypeptide are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide as recited in claims 35, 62, 81, 96, 114, 132, 152, 186, 169, and 205 which are <u>not</u> required to have a function, does not reasonably provide enablement for a nucleic acid encoding a protein comprising less than the full extracellular domain (ECD, amino acids about 52-210 of SEQ ID NO:2) which binds a TNF ligand or less than the full length or mature DR5 protein of SEQ ID NO:2 which induces apoptosis, or as related to claims 190-191 and 204 for polynucleotides which are complementary to a coding polynucleotide but which must encode a

polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to:1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to nucleic acid molecules that are structurally related (either identical or at least 90% identical) to a specific nucleotide sequence or to a nucleotide sequence encoding a specific amino acid sequence. One could make and use a nucleic acid that is structurally related to a nucleic acid that has a particular sequence (e.g., SEQ ID NO:1). However, in the case of ligand binding, only the full extracellular domain has been shown by the inventors (Example 6) to bind a ligand, in the instant example the ligand is TRAIL. The prior art (Chinnaiyan et al., Science, 1996, cited by Applicants) which discloses DR3, shows only that the whole receptor bound another protein (TRADD, p. 991, third paragraph). Also, in the case of induction of apoptosis, only the full-length receptor was shown to be capable of this function in the instant application (Example 5). For the DR3 receptor, it was shown that without the death domain, DR3 could not induce apoptosis (Chinnaiyan et al., p. 992, first paragraph). It is noted that claims, such as claim 67 are drawn to polynucleotides which are not required to encode anything more than amino acids 1-133 of SEQ ID NO:2, and this does not include the death domain and so would not reasonably be expected to induce apoptosis. Similarly, claims such as claim 119 are drawn to polynucleotides which are not required to encode anything more than amino acids 274-340 of SEQ ID NO:2, and this does not include the ECD domain and so would not reasonably be expected to bind a ligand. Because so little was known about how TRAIL-like receptors functioned in terms of ligand binding--both which ligand(s) they bind and what portion(s) of the ECD is necessary for that binding, and how apoptosis is induced in terms of

signal transduction and what portion(s) of both the death domain and the receptor as a whole is necessary for induction of apoptosis, the relative skill of those in the art pertinent to the instant invention is not high.

Further, the specification does not provide guidance about which amino acids within particular domains are necessary for the claimed functions. In view of the lack of information in the prior art and specification, one could not reasonably predict which sequences besides those specifically disclosed in the instant application would have the required functions. The claims have broad breadth because not only are the claimed polynucleotides limited to the complete ECD or full length receptor, for example, but they are drawn to polynucleotides that comprise nucleic acids that are 90% identical to a nucleic acid encoding a specific set of amino acids of SEQ ID NO:2. For these reasons, it would require undue experimentation to make the invention commensurate in scope with the great breadth of the claims.

As to claims 190-191 and 204 as they require encoding of a polypeptide, while polynucleotides which are the coding or "sense" strand can encode a polypeptide as required by these claims, polynucleotides which are the non-coding or "complementary" strand cannot. As a result, it would require undue experimentation to practice the claimed invention commensurate in scope with the claims.

It is noted that if applicants argue that claims drawn to polynucleotides encoding less than the full extracellular domain are enabled for binding a ligand and less than the full length are enabled for inducing apoptosis, then those claims drawn to polynucleotides comprising a nucleic acid encoding amino acids 1-133 or less of SEQ ID NO:2 would be rejectable with the claims below under 102 and 103 as the prior art nucleic acids inherently possessing these characteristics. Rejection under 102 and/or 103 would not necessarily be in lieu of maintaining a rejection under 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

Claims 62, 63, 68, 69, 72-76, 152, 153, 156, 157-164, 169-173, 176, 177, 180-184, 186-

189, 192, 193, 196-200, 205-209, 212, 213 and 216-219 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AA223122 (V).

GenBank Accession No. AA223122 teaches a polypeptide that is 97% identical over nucleotides 236-698 of SEQ ID NO:1 of the instant specification (see "SEQUENCE COMPARISON-B" of paper #6). This region comprises the nucleic acid encoding amino acids 1-333 of SEQ ID NO:2 of the instant application. The nucleic acid of AA223122 is 469 nucleotides long (i.e., the entire length from nucleotides 236-698 of SEQ ID NO:1). Therefore, the nucleic acid would hybridize under conditions set forth in Claim 186 to nucleotides 284-1,362 of SEQ ID NO:1 or to a complement thereof. The nucleic acid is in the Bluescript SK- vector. This vector inherently has the property of being operably linked to a heterologous regulatory sequence (*i.e.*, T3 or T7 promoter) and comprises a heterologous polynucleotide which encodes a heterologous polypeptide, *i.e.*, β-galactosidase. The vector is in the SOLR host cell (see "Source" section). Because of the length of the nucleic acid of AA223122, one would reasonably expect that it encodes at least 7 contiguous amino acids that bind an antibody with specificity for the polypeptide of SEQ ID NO:2.

Claim Rejections - 35 USC § 103

Claims 62, 63, 68, 69, 72-76, 152, 153, 156, 157-164, 169-173, 176, 177, 180-184, 186-189, 192, 193, 196-200, 205-209, 212, 213 and 216-219 as addressed above and claims 70-71, 158-159, 178-179, 185, 194-195, 214-215 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. AA223122 (V) and Chinnaiyan et al. (Science, 1996, cited by Applicants), Sibson et al. (WO 94/01548, N), and Bjorn et al. (V, Current Biol., 1992) in view of Adair et al. (O, WO 91/09967).

GenBank Accession No. AA223122 teaches a polypeptide that is 97% identical over nucleotides 236-698 of SEQ ID NO:1 of the instant specification (see "SEQUENCE COMPARISON-B" of paper #6). This region comprises the nucleic acid encoding amino acids 1-333 of SEQ ID NO:2 of the instant application. The nucleic acid of AA223122 is 469 nucleotides long (i.e., the entire length from nucleotides 236-698 of SEQ ID NO:1). Therefore,

the nucleic acid would hybridize under conditions set forth in Claim 186 to nucleotides 284-1,362 of SEQ ID NO:1 or to a complement thereof. The nucleic acid is in the Bluescript SK- vector. This vector inherently has the property of being operably linked to a heterologous regulatory sequence (*i.e.*, T3 or T7 promoter) and comprises a heterologous polynucleotide which encodes a heterologous polypeptide, *i.e.*, β-galactosidase. The vector is in the SOLR host cell (see "Source" section). Because of the length of the nucleic acid of AA223122, one would reasonably expect that it encodes more than 7 contiguous amino acids that bind an antibody with specificity for the DR5 polypeptide of SEQ ID NO:2. The nucleic acid is classified as an EST (see "Division Code"). GenBank Accession No. AA223122 does not teach production and recovery of an encoded polypeptide or fusion to a polynucleotide encoding a human immunoglobulin Fc region (Ig-Fc).

Chinnaiyan et al. teach vectors comprising the DR3 receptor-encoding nucleic acid, transfection of mammalian cells, and expression followed by recovery of the receptor by FLAG immunoprecipitation (see legend of Figure 3B). It was also shown that without the death domain, DR3 blocked DR3-induced apoptosis (Chinnaiyan et al., p. 992, first paragraph).

Sibson et al. teach the desirability of expressing ESTs. It is stated (p. 10, line 38) that "Partial or full length cDNAs have great utility once expressed." And (p. 11, lines 9-10), "The proteins thus-expressed can be screened for activities of therapeutic or commercial value." Also taught is that fragments as short as 8 amino acids in length can be used as antigens for the production of useful antibodies (p. 11, lines 16-22). Also taught is an EST library formed by ligating each DNA piece into a pBluescript vector and transformation of *E. coli* host cell DH5a (p. 19, third paragraph). All methods of expression described by Sibson et al. are old in the art (*e.g.*, p. 8, lines 26-34).

Bjorn et a. teach the advantages of fusion proteins comprising Ig-Fc. On page 571, third paragraph, it is stated that "Capon and co-workers [10] showed that by fusing the CD4 derivative to the Fc portion of immunoglobulin G (IgG), the serum half-life of CD4 in rabbits increased 200-fold. This result demonstrates that a rapidly cleared protein can be stabilized by fusion to a carrier which is more stable *in vivo*."

Adair et al. teach humanized antibodies and that non-human antibodies are antigenic in humans and lead to an undesirable immune response (p. 2, beginning of third paragraph).

It would have been obvious to express and recover the polypeptide encoded the nucleic acid of GenBank Accession No. AA223122 because Chinnaiyan et al. teach methods of expressing nucleic acids and recovering the products, and Sibson et al. also teach methods as well as the desirability of obtaining such expressed polypeptides, for example for use as antigens. If further would have been obvious to produce the encoded protein as fused to a human Ig-Fc region because Bjorn et al. teach this increases the half-life of the non-Fc protein and Adair et al. teach that using human Ig-Fc will not lead to an undesirable immune response in humans. This would be desirable if one sought to use the DR5 polypeptide without the death domain as a means to inhibit apoptosis in humans as suggested by Chinnaiyan et al. for the function of the DR3 deletion construct used *in vitro*.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Wiley et al. (A, US Patent 5,763,223) describe the cytokine TRAIL, also known as Apo-2 ligand, to which trail binding proteins like DR5 can bind. Stratagene Cloning Systems 1994 catalogue (W) describes the Bluescript SK- vector.

Term Usage

It is noted that the art also refers to DR5 as Apo-2, TR6 and TRAIL-2.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

cmk

January 14, 2000

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER